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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 66)

Date of mailing *(day/month/year)*	22.08.2005
Applicant's or agent's file reference ./.	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/051922	30.09.2004	08.10.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/4035, C07D209/46, A61P7/02, C07D401/06, C07D413/04

Applicant
NICHOLAS PIRAMAL INDIA LIMITED et al.

1. ☒ The written opinion established by the International Searching Authority:
   ☒ is ☐ is not
   considered to be a written opinion of the International Preliminary Examining Authority
2. This second report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
   Also: For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.
   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 08.02.2006

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WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/IB2004/051922

IAP9 Rec'd PCT/PTO 07 APR 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this opinion is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-142	as originally filed

Claims, Numbers

1-20	as originally filed
23, 24	received on 11.05.2005 with letter of 06.05.2005

Drawings, Sheets

1/10-10/10	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 21 and 22
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 23 and 24
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21, 22; all claims with respect to prodrugs; 1,2,4-6 and claims referring thereto (part not comprised in claim 3)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search opinion has been established for the said claims Nos. as above

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See supplemental sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. Consequently, this opinion has been established in respect of the following parts of the international application:

☐ all parts.

☒ the parts relating to claims Nos. . 1-20

Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,5-9
	No:	Claims	1,2,4,10-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations:

see separate sheet

Re Item I

The amendments filed with the letter dated 06.05.2005 introduce subject-matter which extends beyond the content of the application as filed, contrary to Articles 19(2) and 34(2)(b) PCT. The amendments concerned are the following:

- Newly filed claim 23 appears to be based on originally filed claim 21 turned into a claim dependent on claim 10. Claim 23 refers to intermediate H-63, which is not defined.

- Newly filed claim 24 appears to be based on originally filed claim 22 turned into a claim dependent on claim 10. In originally filed claim 22, R' is "H, a protected amino group or a leaving group" whereas in newly filed claim 24 R' is $-NH_2$ (cf. claim 10, formula (III)). An additional step has also been added to newly filed claim 24 compared to former claim 22, namely, "optionally, deprotecting the amine group".

Consequently, this examination is being performed on the claims as originally filed.

Should amendments be filed in response to this written opinion, these will only be taken into account when the applicant identifies clearly all amendments made (e.g. by submitting one set of originally filed pages with hand-written amendments) and indicates on which passages of the original application these amendments are based (Rule 66.8 PCT).

Re Item III

1. The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of claims 1 and 2 (for examples, see search report). So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). In addition, present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.

For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been carried out for compounds according to claim 3, i.e. where there is at least one substituent of formula (5) at R^G.

2. The present claims do not fulfil the requirements of Articles 5 and 6 PCT to such an extent as to render a meaningful search impossible. It is unclear which technical features are necessary to perform the functional term "prodrug" and thus which specific compounds fall within the scope of the present claims. Moreover, this functional definition is a mere invitation to the skilled person to perform a research program in order to find the suitable variants (cf. definition in description p. 15). The invention cannot be carried out over the whole claimed area without imposing an undue burden on the skilled person, and the disclosure is thus considered to be insufficient. Consequently, the search did not include prodrugs of the compounds of formula I.

Re Item IV

This Authority found multiple inventions in this international application, as follows:

1. Claims 1-20
   Compounds of formula I and corresponding syntheses, compositions and uses thereof

2. Claim 21
   Alternative process for introducing a keto substituent at the *ortho* position of phenols.

3. Claims 22
   Alternative process for introducing a keto substituent at the *para* position of phenols.

The problem underlying the first group lies in the provision of further fibrinogen receptor antagonists (see present description, p. 1, lines 5 - 9), whereas the problems underlying groups 2 and 3 lies in the provision of alternative syntheses of keto-substituted phenols. Two different problems are thus addressed that are not so linked to form a single general inventive concept (Rule 13.1 PCT).

The only feature common to the processes of groups 2 and 3 is that keto-substituted phenols are produced in both cases. Since such compounds are well known in the art (see e.g. WO-A-02 085855, scheme CO-1), it follows that this feature cannot be considered as being a special technical feature within the meaning of Rule 13.2 PCT. Groups 2 and 3 are therefore also not linked by a single general inventive concept (Rule 13.1 PCT).

Re Item V

1. Reference is made to the following documents:
   D1: EP-A-0 655 439
   D2: WO-A-02 085855 (family member, P-document: EP-A-1 391 451)
   D3: EP-A-0 540 334 D4: US-A-3 997 572
   D5: DD-A-66 175 D6: GB-A-989 917
   D7: J. Med. Chem., vol. 29, no. 8, 1986, pages 1476-1482
   D8: J. Med. Chem., vol. 35, no. 24, 1992, pages 4542-4548

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 2, 4 and 10-20 is not new in the sense of Article 33(2) PCT:

   Documents D2 discloses numerous imino-isoindole derivatives falling within the scope of present claims 1, 2 and 4 (for claim 4 see numerous compounds e.g. example 546 containing a phenoxy acetic acid moiety or homologues thereof; cf. present formula (5)). The compounds of present claim 3, 5 and 6 differ from those of D2 because Y^1/Y^2 are =O/S.

   The compounds of D3 wherein X is a cyclic moiety are considered to fall within the scope of claims 1 and 2 owing to the passage in the present description (p. 13, lines 4-8) that alkyl groups, unless stated otherwise, may be optionally substituted. Thus, many of the compounds in claim 4 of D3 fall within the scope of present claims 1 and 2 (cf. present R^A is $-C(=O)-NR^1R^2$ wherein R^1 is a substituted alkyl). The compounds of D3 are fibrinogen receptor antagonists (see claim 13).

   Documents D4 - D8 disclose a number of pharmaceutically active compounds falling within the scope of present claims 1 and 2 (see references in search report).

3. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of the present claims does not involve an inventive step in the sense of Article 33(3) PCT.

Document D1, which is regarded as being the closest prior art, discloses fibrinogen receptor antagonists (p. 1, lines 23-26). Formula I of D1 overlaps with present formula I. D1 teaches the presence of a 5,6-bicyclic scaffold whereby the 5-membered ring is attached to an acidic group via an optional linker and the 6-membered ring is attached to a basic group via an optional linker. The present exemplified 1-oxo-1,3-dihydroisoindol-2-yl moiety is specifically suggested in D1 (see p. 17, line 45). It would therefore have been obvious for the person skilled in the art, faced with the problem of providing further fibrinogen receptor antagonists, to further modify the exemplified compounds of D1 according to the above teaching in order to arrive at the present compounds.

An inventive step cannot therefore be acknowledged, in the absence of evidence showing that substantially all the claimed compounds have an unexpected property or improved activity with respect to the structurally closest prior art compounds of D1, attributable to the distinguishing feature of the invention.